British Heart Journal, 1973, 35, 743–751.

Haemodynamic effects of a new beta-blocking agent 'Sectral' (M & B 17803A)

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The haemodynamic effects of a new beta-blocking agent, 'Sectral' (M & B 17803A) were measured in 5 patients with coronary artery disease, 5 patients with regional left ventricular asynergy, and in 4 control subjects. The drug was given as a single intravenous dose of 10 mg and then an additional 20 mg.

A negative chronotropic effect was observed in all the patients and their heart rate fell by 2 to 15 per cent. Left ventricular contractility was reduced and there was a decrease in peak LVdp/dt (15 to 23%), peak V_{ce} (4 to 14%), and in V_{max} (14 to 18%). The left ventricular end-diastolic pressure (LVEDP) increased slightly and this effect was greater in the patients with regional fibrosis of the left ventricle. There was a slight decrease in stroke index (SI) (0 to 10%) and cardiac index (CI) fell by 7 to 21%.

Sectral, M & B 17803 (DL-1-(2-acetyl-4-butyramidophenoxy)-2-hydroxy-3-isopropylaminopropane hydrochloride), is a new cardioselective beta adrenergic antagonist. It blocks the myocardial $beta_1$ receptors by competitive inhibition and has in addition a membrane stabilizing and quinidine-like effect; it also has a weak inherent sympathomimetic action (May and Baker, Dagenham, England, 1971, personal communication). There is a small effect on peripheral vascular dynamics, and the drug may produce a minor fall in arterial pressure and limb blood flow (C. F. George, R. A. Briant, F. Fenyvesi, and C. T. Dollery, 1971, personal communication); there is little or no effect on the bronchial $beta_2$ receptors.

Preclinical studies have shown that the drug is well absorbed orally and has a plasma half-life of 1·8 hours. The beta-blocking effect is more prolonged and the pharmacological half-life is 10 to 12 hours (May and Baker, 1971, personal communication).

Intravenous administration has been used in various animal experiments to assess its beta-blocking effect: it is 1/4–1/7 as potent as propranolol, 0·09 mg/kg produces a 50 per cent decrease in isoprenaline-induced tachycardia (as assessed by standard log-dose response curves) and 1·0 mg/kg produces complete blockade in the anaesthetized cat. It is slightly more potent than practolol in inhibiting this response but propranolol is more effective: a dose of propranolol of 0·03 mg/kg produces complete beta blockade (May and Baker, 1971, personal communication).

The present study was undertaken to examine the beta-blocking effect and haemodynamic changes produced by intravenous Sectral in man.

Patients

Three groups of patients were studied. Their clinical, electrocardiographic, radiological, and angiographic data are shown in Table 1.

Group 1: Five patients had coronary artery disease without important regional ventricular dysfunction.

Group 2: Five patients had regional left ventricular asynergy with angiographic akinesis or dyskinesis or frank aneurysm formation (Gorlin, Klein, and Sullivan, 1967). In 4 patients the aneurysm was the result of coronary artery disease and previous myocardial infarction; one patient had normal coronary arteries.

Group 3: Four patients in whom there were reasons for suspecting myocardial disease were investigated, 2 of them by cardiac catheterization; as it turned out myocardial disease was not found in any of them and they could be regarded as normal controls.

Chemotherapy

Patients with chest pain continued to take trinitrin or isosorbide-dinitrate. The patients were not receiving digitalis at the time of study. Drugs acting on the autonomic nervous system were withdrawn 5 to 7 days before catheterization.

Received 7 August 1972.

TABLE I *Patients*

	Age (yr)	*Sex*	*Race*	*Angina*	*Previous infarction*	*Other symptoms*	*Electrocardiogram*	*CTR*
Group 1: coronary artery disease								
1	51	M	Europ.	Yes	Yes (1 episode)	—	Diaphragmatic infarction	0·46
2	51	M	Europ.	Yes	—	—	Ischaemia	0·45
3	48	M	Europ.	Yes (decubitus)	Yes (1 episode)	—	Ischaemia; RBBB + lt. anterior hemiblock	0·47
4	37	M	Europ.	Yes	—	—	Atrial rhythm	0·48
5	41	M	Europ.	Mild	Yes (1 episode)	Vineberg procedure 1969	Anterolateral LV damage	0·45
Group 2: LV aneurysm								
6	38	M	Asian	—	Yes (3 episodes)	Arrhythmias	Anteroseptal infarction; lt. anterior hemiblock; numerous prem. vent. contractions	0·53
7	39	M	Europ.	—	Yes (3 episodes)	—	Extensive anterior infarction; prem. ventric. contraction	0·48
8	49	M	Asian	Yes	Yes (2 episodes)	Arrhythmias and dizziness	Diaphragmatic infarction; prem. atrial contractions	0·75
9	33	M	Asian	Yes	Yes (1 episode)	—	Pattern of anterior infarction	0·41
10	52	M	Asian	Yes	Yes (4 episodes)	—	Extensive anterolateral and diaphragmatic infarction; lt. posterior hemiblock	0·59
Group 3: control subjects								
11	30	M	Asian	—	—	Aortic aneurysm	Normal	0·46
12	33	M	Europ.	—	—	Nonspecific chest pain	Mild LV hypertrophy	0·52
13	50	F	Asian	—	—	Chest pain; atrial septal defect repair 1960	Prem. atrial contractions; digitalis effect	0·61
14	17	M	Asian	—	—	Syncope	Wolff-Parkinson-White syndrome	0·42

CTR = cardiothoracic ratio; RBBB = right bundle-branch block; + = obstructed coronary artery.

Methods

Routine cardiac catheterization was performed through a percutaneous puncture of the right and left femoral arteries and veins. Premedication with 10 mg diazepam and 50 mg pethidine was given 1 hour before the study. Intravascular pressures were measured through Statham P23 Db bonded strain gauges using the midchest level as the zero reference. Cardiac output was measured in duplicate by the indicator dilution method. Indocyanine green, 5 mg, was injected into the main pulmonary artery: samples were taken from the descending aorta using a constant withdrawal Harvard infusion pump at a rate of 38 ml/min. The concentration of green dye was measured with a Gilford optical densitometer and cardiac output calculated using the Stewart-Hamilton principle (Hamilton, 1953).

Myocardial contractility was assessed from a high speed recording (200 mm/sec) of the left ventricular (LV) pressure and its first derivative using an electronic analogue differentiating amplifier without phase lag or distortion. Peak LVdp/dt was measured (Mason, 1969). Force-velocity curves were constructed for each patient and for normal subjects according to the method of Mason, Spann, and Zelis (1970) (Bakst, Lewis, and Gotsman, 1972). The velocity of shortening of the contractile element was derived from the formula $V_{ce}=\frac{dp/dt}{32P}$, which is based on the assumption that during isovolumic systole the velocity of the contractile element (V_{ce}) is equal to the velocity of the series elastic element (V_{se}). The force-velocity curve constructed in this way has three components: an ascending limb (from zero velocity at LV end-diastolic pressure), a clearly defined point of inflexion, and a descending limb where velocity decreases as the pressure and load increases. The ascending limb of the curve depends on the preload, the inertia of the system, and the V_{ce}; the point of inflexion represents the true peak velocity. Retrograde extrapolation of the descending limb to zero load defines V_{max}. Though the ideal force-velocity curve is hyperbolic, linear extrapolation was used in this study to simplify the calculation since insufficient points were measured during a single systole to construct a representative hyperbola. In each patient peak velocity and V_{max} were calculated.

The systolic time intervals of the cardiac cycle were

Left ventriculogram (Gorlin *et al.*, 1967)	*Coronary angiography*		
	Rt. coronary artery	*Anterior descending*	*Circumflex*
Normal	+(90%)	+(30%)	+(30%)
Normal		+(100%)	+(100%)
Diaphragmatic asyneresis (minimal)	+(100%)	+(70%)	+(90%)
Normal	+(40%)	+(90%)	
Normal		+(100%)	+(100%)
Anterior dyskinesis	+(100%)	+(100%)	
Anterior dyskinesis	+(80%)	+(100%)	+(90%)
Diaphragmatic akinesis	+(100%)	+(80%)	+(100%)
Anterior akinesis; apical thrombus	Normal		
Hypokinesis of LV; diaphragmatic akinesis	+(70%)	+(100%)	+(100%)
Normal	Not done		
Normal	Normal		
Normal	Normal		
Normal	Not done		

measured from the electrocardiogram, phonocardiogram, and a simultaneous pressure recording in the ascending aorta. The delay time of the catheter manometer system was determined from a comparison of the dicrotic notch of the aortic pressure tracing with the aortic component of the second heart sound and the appropriate correction made in the measurements. The systolic time intervals have two components: pre-ejection phase (PEP), from the earliest q wave of the electrocardiogram to the instant of aortic pressure rise, and left ventricular ejection time (LVET) from aortic valve opening to its closure. The PEP/LVET ratio was also calculated – this ratio correlates with LV ejection fraction (Garrard, Weissler, and Dodge, 1970).

Routine cardiac catheterization was followed by left ventricular cineangiography in the right anterior oblique view using 50 ml of 76 per cent Urografin. Selective coronary angiography was performed in several oblique views in 12 patients (Judkins, 1967). The patients were allowed to rest after the angiographic manipulations.

Control measurements were made at least 15 minutes after angiography: they were cardiac index, stroke index, heart rate, left ventricular and arterial pressures, LVdp/dt, peak V_{ce}, and V_{max}. The systolic time intervals were also measured.

The patients were then given 10 mg Sectral intravenously and the haemodynamic measurements repeated after 10 minutes. A further dose of 20 mg Sectral was then given (total dose of 30 mg beta-blocker) and 10 minutes later measurements were again made.

Finally, the patients were challenged with 10 μg isoprenaline sulphate intravenously to see whether beta-blockade could be reversed. In 4 subjects, isoprenaline sulphate was also given before the beta-blocking drug so that the efficacy of beta-blockade could be assessed for the dosage used in this study.

Critique of methods

A fluid-filled catheter manometer system was used for pressure measurements: this provides reliable routine intravascular measurements but the frequency response of the system may distort the high frequency components of the pressure measurements and differentiation exaggerates the error (Yanof *et al.*, 1963; Gersh, Hahn, and Prys-Roberts, 1971). The results are different if a catheter-tip micromanometer is used. For this reason peak V_{ce} and V_{max} were only measured in patients who had technically perfect pressure recordings. Moreover, while the velocity of contractile fibre shortening is readily measured *in vitro*, the validity of applying the technique to the intact man is under debate (Mason *et al.*, 1970; Sonnenblick, Parmley, and Urschel, 1969; Pollack, 1970; Noble, 1972). Finally, we clearly recognize that the series elastic element may be different in normal subjects and in patients with cardiac disease – particularly left ventricular aneurysm – and the constant 32, which is used in the calculation of V_{max}, may not always be correct (Sonnenblick, 1964; Parmley and Sonnenblick, 1967, 1971).

Results

The haemodynamic measurements before and after the pharmacological interventions are shown in Table 2 and the percentage changes are shown in Table 3.

Heart rate

Sectral decreased heart rate in all three groups of patients: after 10 mg of the drug heart rate fell by 4 per cent in patients with coronary artery disease, 15 per cent in patients with aneurysm, and 14 per cent in the control subjects. After the larger dose, the mean percentage change in each group was smaller, i.e. −2 per cent in Group 1, −8 per cent in Group 2, and −11 per cent in the control subjects (Fig. 1).

The beta-blocking effect could be overcome in all patients by 10 μg isoprenaline sulphate but the tachycardia produced was mild: it was less than the comparative tachycardia induced before administra-

TABLE 2 *Haemodynamic measurements*

	*Experimental situation**	*Heart rate/ min*	*Stroke index (ml/beat/ m²)*	*Cardiac index (l./min per m²)*	*LVEDP*	*Mean arterial pressure (mmHg)*	*Peak LVdp/dt*	*Peak V_{ce}*	*V_{max}*	*PEP*	*LVET*	*PEP/ LVET*
Group 1: coronary artery disease												
1	Control	87	23	2·0	10	82	1962	0·81	1·43	95	270	0·35
	S 10 mg	78	26	2·0	20	83	1445	0·73	0·97	91	292	0·32
	S 30 mg	77	28	2·2	25	85	1269	0·61	1·07	88	295	0·30
	Isoprenaline	100	—	—	10	76	1269	—	—	60	240	0·25
2	Control	68	32	2·2	18	99	1540	0·81	1·03	110	310	0·35
	S 10 mg	64	33	2·1	15	88	1480	0·87	1·08	100	295	0·32
	S 30 mg	71	30	2·1	10	93	1510	0·85	1·08	105	285	0·30
	Isoprenaline	82	—	—	10	55	1670	1·34	1·75	95	265	0·25
3	Control	80	—	—	30	100	—	0·84	1·10	—	—	—
	Isoprenaline	128	—	—	26	98	—	0·99	1·47	—	—	—
	Control	91	34	3·1	28	104	1540	0·73	1·10	70	307	0·23
	S 10 mg	82	31	2·6	26	105	1440	0·60	0·80	92	325	0·28
	S 30 mg	76	31	2·3	25	99	1060	0·56	0·78	95	335	0·28
	Isoprenaline	92	—	—	27	104	1380	0·70	1·42	67	285	0·24
4	Control	72	—	—	20	107	2120	—	—	85	275	0·31
	Isoprenaline	94	—	—	16	90	3140	—	—	50	200	0·25
	Control	75	34	2·6	14	112	2260	—	—	90	270	0·33
	S 10 mg	83	29	2·4	12	106	1930	—	—	90	260	0·35
	S 30 mg	88	24	2·1	12	104	1840	—	—	95	250	0·38
	Isoprenaline	103	—	—	12	99	3320	—	—	55	250	0·22
5	Control	78	—	—	—	—	—	0·69	0·90	—	—	—
	Isoprenaline	110	—	—	—	—	—	1·00	1·20	—	—	—
	Control	78	32	2·5	14	92	1810	—	—	95	280	0·34
	S 10 mg	75	25	1·9	9	77	1390	—	—	90	280	0·32
	S 30 mg	77	28	2·1	14	85	1300	—	—	90	280	0·32
	Isoprenaline	92	—	—	—	79	—	—	—	80	250	0·32
Group 2: LV aneurysm												
6	Control	110	28	3·1	15	65	785	0·69	0·96	165	185	0·89
	S 10 mg	104	31	3·2	15	78	695	0·61	0·80	170	200	0·85
7	Control	77	45	3·5	20	76	695	—	—	120	290	0·41
	S 10 mg	60	42	2·5	30	93	—	—	—	120	310	0·39
	S 30 mg	63	38	2·4	20	86	665	—	—	120	310	0·39
	Isoprenaline	69	—	—	28	89	965	—	—	110	290	0·38
8	Control	75	24	1·8	—	—	1721	0·83	—	99	209	0·38
	S 10 mg	73	28	2·1	—	—	1389	0·76	—	102	210	0·49
	S 30 mg	85	22	1·8	—	—	1268	0·75	—	96	260	0·37
9	Control	82	37	3·0	15	87	1690	0·95	1·90	100	280	0·36
	S 10 mg	65	39	2·6	27	76	1360	0·75	1·68	95	275	0·35
	S 30 mg	63	39	2·5	20	77	1290	0·77	1·73	115	275	0·42
	Isoprenaline	75	—	—	10	74	2000	—	—	100	235	0·43
10	Control	72	33	2·4	16	91	1660	0·82	1·60	110	240	0·46
	S 10 mg	71	28	2·0	17	87	1200	0·68	1·27	105	230	0·46
	S 30 mg	69	27	1·9	15	92	1050	0·74	1·25	120	210	0·57
	Isoprenaline	90	—	—	10	88	1910	—	—	120	195	0·61
Group 3: control subjects												
11	Control	100	—	—	10	92	1660	0·82	1·97	105	245	0·43
	S 10 mg	103	—	—	13	94	1510	0·81	—	90	240	0·38
	S 30 mg	100	—	—	15	94	1750	0·84	1·97	100	240	0·42
12	Control	78	35	2·7	10	84	1930	0·99	—	75	260	0·29
	S 10 mg	62	38	2·4	10	80	1600	0·94	—	70	270	0·26
	S 30 mg	60	40	2·4	10	76	1530	0·90	—	80	280	0·29
13	Control	82	38	3·1	13	92	1620	0·88	1·50	95	325	0·29
	S 10 mg	73	33	2·4	14	90	1180	0·72	1·26	105	330	0·32
	S 30 mg	71	32	2·2	14	94	935	0·68	1·08	125	330	0·38
	Isoprenaline	87	—	—	5	84	1970	1·16	1·26	90	305	0·30
14	Control	69	—	—	15	77	1570	0·72	—	95	305	0·31
	Isoprenaline	133	—	—	10	71	2810	1·23	—	55	190	0·29
	Control	87	41	3·6	13	78	1630	0·73	—	70	290	0·24
	S 10 mg	65	40	2·6	13	74	1390	0·69	—	70	315	0·22
	S 30 mg	71	37	2·7	10	76	1540	0·84	—	80	310	0·26
	Isoprenaline	90	—	—	10	70	2420	1·10	—	60	240	0·25

LVEDP = left ventricular end-diastolic pressure (mmHg); LVET = left ventricular ejection time (msec); PEP = pre-ejection phase (msec); V_{ce} = velocity of the contractile element (muscle lengths/sec); $V_{max} = V_{ce}$ at zero load (muscle lengths/sec).
* S = Sectral.

TABLE 3 *Mean percentage changes after Sectral*

Dose	*Group 1: coronary artery disease*		*Group 2: LV aneurysm*		*Group 3: control*	
	10 mg	*30 mg*	*10 mg*	*30 mg*	*10 mg*	*30 mg*
Heart rate	−4 (−10 to +12)	−2 (−17 to +17)	−15 (27 to −1)	−8 (−4 to +13)	−14 (−25 to +1)	−11 (0 to −23)
Stroke index	−6 (−22 to +13)	−8 (−30 to +22)	0 (−16 to +14)	−10 (−17 to +5)	−1 (−12 to +9)	−3 (−16 to +15)
Cardiac index	−9 (−24 to +2)	−10 (−25 to +9)	−7 (−29 to +11)	−18 (−31 to −2)	−20 (−27 to −13)	−21 (−25 to −11)
LV end-diastolic pressure	+5 (−36 to +100)	+16 (−44 to +150)	+34 (0 to +80)	+9 (−6 to +33)	+6 (−8 to +30)	+5 (−23 to +50)
Mean arterial pressure	−6 (−16 to +1)	−4 (−8 to +4)	+6 (−13 to +22)	+1 (−12 to +13)	−3 (−5 to +2)	−2 (−10 to +2)
Peak LVdp/dt	−15 (−26 to −7)	−23 (−35 to −2)	−17 (−23 to −12)	−21 (−28 to −4)	−17 (−27 to −9)	−16 (−42 to +5)
Peak V_{ce}	−7 (−18 to +7)	−14 (−25 to +5)	−14 (−21 to −8)	−13 (−19 to −10)	−8 (−18 to −1)	−4 (−23 to +15)
V_{max}	−18 (−32 to +5)	−17 (−29 to +5)	−16 (−21 to −12)	−15 (−22 to −9)	−15 (−23 to −5)	−14 (−32 to 0)
Pre-ejection phase (PEP)	+3 (−9 to +31)	+6 (−7 to +36)	−1 (−5 to +3)	+5 (−3 to +15)	−3 (−14 to +11)	+12 (−5 to +32)
LV ejection time (LVET)	+1 (−5 to +8)	+1 (−8 to +9)	+1 (−4 to +8)	+4 (−13 to +20)	+3 (−2 to +9)	+4 (−2 to +8)
PEP/LVET	+2 (−9 to +22)	+5 (−6 to +22)	−3 (0 to −5)	+8 (−3 to +24)	−5 (−12 to +10)	+9 (−2 to +31)

The range of value is given in brackets.
Same abbreviations as Table 2.

tion of the beta-blocking drug. This indicates that effective beta-blockade had been produced.

Stroke index

Stroke index fell slightly in all three groups of patients (Fig. 2). The change was related to dose. The greatest change was seen in the patients with LV aneurysm after administration of 30 mg Sectral (−10%).

Cardiac index

The cardiac index fell by 10 to 21 per cent in the 3 groups (Fig. 3). Ten mg of the drug produced a significant change in cardiac index, but the effect was related to dose in patients with ventricular asynergy, and in them a further fall in output occurred after the larger dose.

LV contractility

LV contractility was depressed. After 30 mg Sectral LVdp/dt fell by 23 per cent in Group 1, 21 per cent in Group 2, and 16 per cent in Group 3 (Fig. 4).

$Peak_{ce}$ and V_{max} were also diminished: peak V_{ce} fell by 14 per cent in Group 1, 13 per cent in Group 2, and 4 per cent in Group 3, while V_{max} fell by 17 per cent in Group 1, 15 per cent in Group 2, and 14 per cent in the control subjects (Fig. 5).

Myocardial contractility was improved by the isoprenaline challenge; there were insufficient measurements to make a meaningful comparison of the response to isoprenaline before and after Sectral.

LV end-diastolic pressure

The change in end-diastolic pressure varied. Though the overall mean pressure increased, LV end-diastolic pressure fell in half the patients in Group 1 and Group 3; it always increased in patients with regional asynergy and left ventricular fibrosis.

Mean arterial pressure

There was little change in mean arterial pressure after the beta-blocker: there was a small decrease in arterial pressure in Groups 1 and 3, and there was a small increase in patients with left ventricular aneurysm after the smaller dose of the drug (Fig. 6).

Systolic time intervals

Pre-ejection phase (PEP) was slightly prolonged in all three groups of patients after administration of Sectral, a consequence of the reduced contractility and decreased LVdp/dt. LVET was essentially unchanged in this study. The PEP/LVET ratio varied, but in general there was a small increase in this measurement (5% in Group 1, 8% in Group 2,

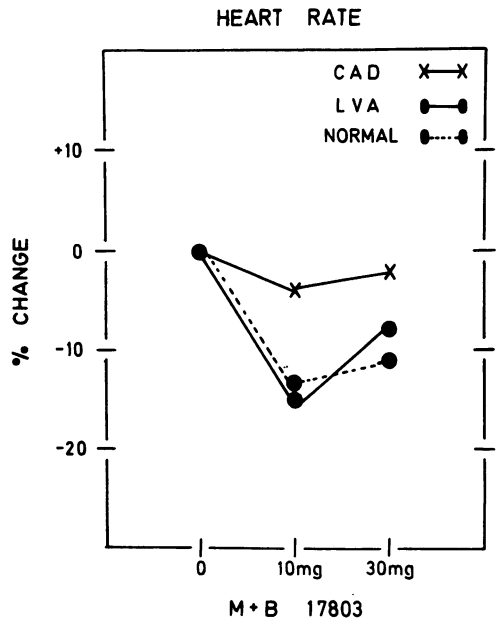

FIG. 1 *Mean percentage change in heart rate (HR) after M & B 17803 (Sectral). Heart rate falls by 4 per cent (range −10 to +12%) in patients with coronary artery disease (CAD), by 15 per cent (range −27 to −1%) in patients with left ventricular asynergy (LVA), and by 14 per cent (range −25 to +1%) in normal controls after 10 mg of the drug. Absolute values and the range of measurements are given in Table 3.*

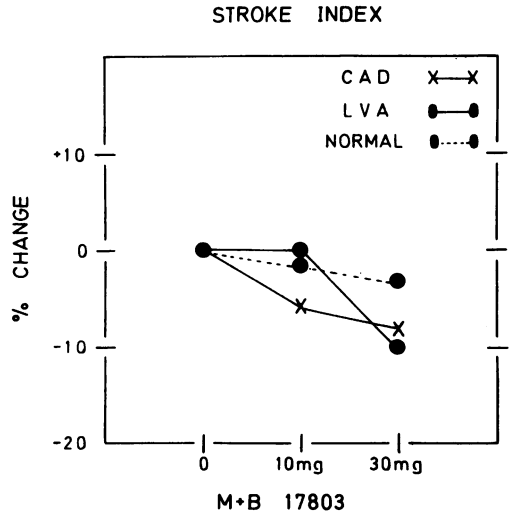

FIG. 2 *Mean percentage change in stroke index (SI) after Sectral. There is a small decrease in stroke index and this is dose-dependant.*

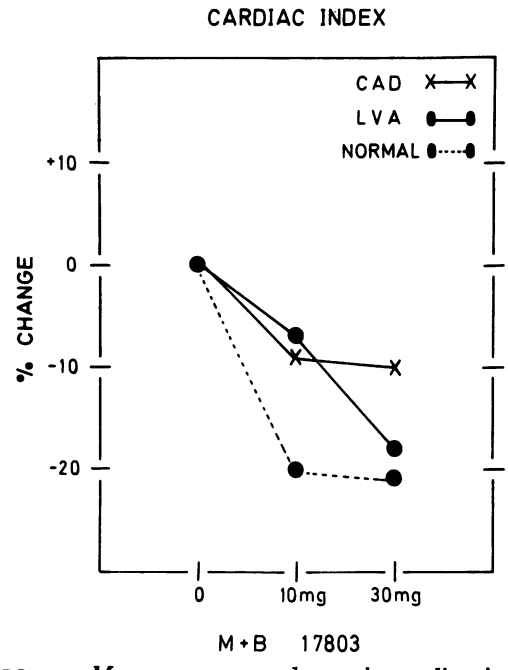

FIG. 3 *Mean percentage change in cardiac index (CI) after intravenous Sectral. There is a dose-dependant decrease in cardiac index.*

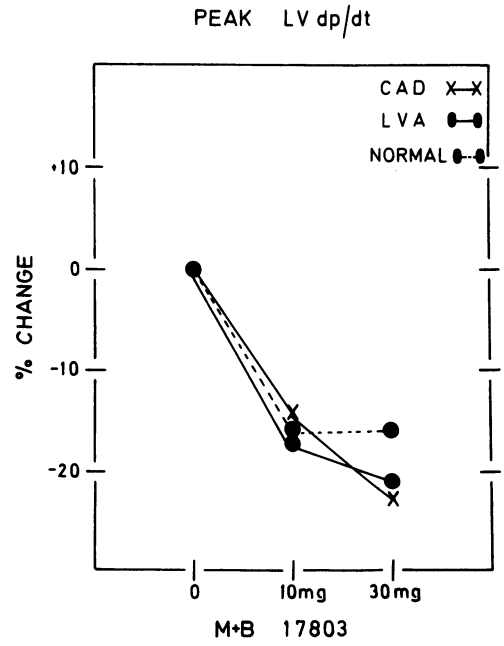

FIG. 4 *Mean percentage change in LVdp/dt after Sectral. 10 mg Sectral produced a decrease in LVdp/dt. There was little further change after the larger dose.*

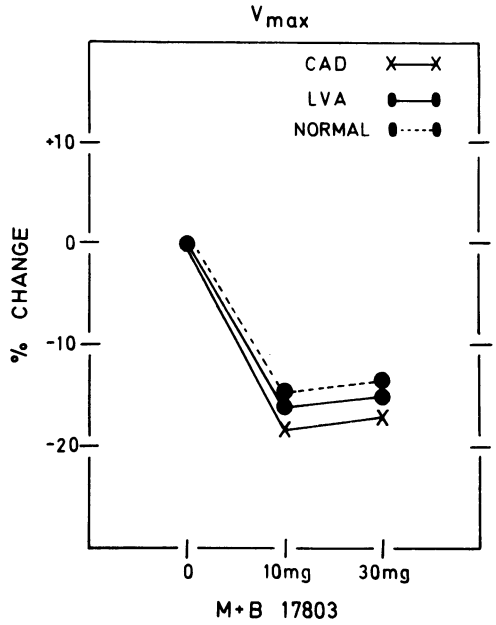

FIG. 5 *Mean percentage change in V_{max} after Sectral in 3 groups of patients.*

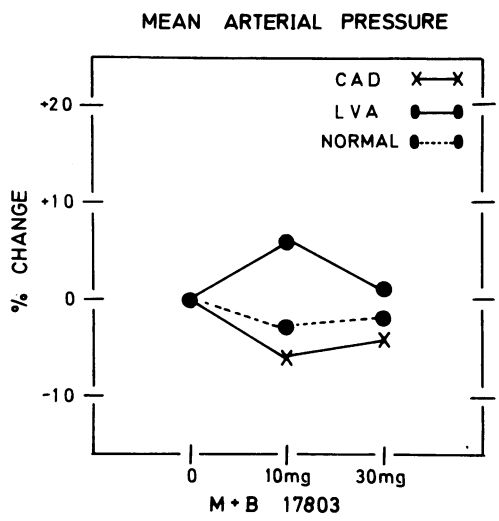

FIG. 6 *Mean percentage change in mean arterial pressure (MAP) after Sectral. The mean arterial pressure was essentially unaltered.*

and 9% in Group 3). This indicates that there was a small decrease in LV ejection fraction after administration of Sectral (Garrard *et al.*, 1970).

Discussion

Beta adrenergic blocking agents

Beta adrenergic blocking agents are now widely used in the management of angina pectoris, arrhythmias, hypertension, thyrotoxicosis, and anxiety states. Propranolol is the prototype beta antagonist but it produces widespread beta-blockade: it blocks bronchial $beta_2$ receptors and is therefore of limited value in patients with pulmonary disease. It also has a membrane stabilizing and cardiac depressant action ('quinidine-like' effect). This effect may be desirable in the management of certain arrhythmias but it further reduces cardiac and stroke output (Brunner, Hedwall, and Meier, 1971).

The newer beta adrenergic antagonists aim at cardioselectivity, so that, in ideal circumstances, bronchial and arteriolar $beta_2$ receptors are undisturbed. Fortunately several of these drugs have intrinsic sympathomimetic activity so that the net effect on cardiac output is negligible. Table 4 summarizes the actions of the beta-blocking agents in current use (Epstein and Braunwald, 1966, 1967; Ablad, Brogard, and Ek, 1967; Grandjean and Rivier, 1968; Waal, 1968; Wilson *et al.*, 1968; Dollery, Paterson, and Conolly, 1969; Brunner *et al.*, 1970; Meier, 1970; Rivier, Nissiotis, and Jaeger, 1970; Bensaid, Scebat, and Lenegre, 1970; Taylor,

TABLE 4 *Beta-blocking drugs in current use*

Drug	*Beta-blockade*			*Sympatho-mimetic*	*Membrane effects*	*Relative oral dose*
	Myocardium (β1)	*Peripheral vascular*	*Bronchial (β2)*			
Propranolol	++	+++	+++	−	+	1
Oxprenolol	++	+	+	+	+	1
Alprenolol	++	+	+	+	+	1
Practolol	++	−	−	+	−	10
Sotalol	++	+		−	−	10
Sectral	++	+ (Dollery*)	±	+	+	7·5 (May and Baker†)

* Dollery *et al.* (1969). † May & Baker (personal communication).

Majid, and Sharma, 1970; Prichard, Aellig, and Richardson, 1970; Barrett, 1971; McNeill, 1971; Gibson, 1971; Kerber *et al.*, 1972; Finegan, Marlon, and Harrison, 1972; Gibson and Coltart, 1972). Sectral appears to combine the cardioselectivity of practolol with the membrane stabilizing effect of propranolol. Preliminary studies have shown it to be effective in the management of angina pectoris and, by virtue of its membrane effects, for the control of arrhythmias, including digitalis induced arrhythmias (May and Baker, 1971, personal communication).

Published reports

The actions and uses of the different blocking agents have been studied in great detail and formed the subject of many reports. Difficulties have been introduced as different methods are used to assess the efficacy of beta-blockade. The dose of the drugs used and the routes of administration have varied in each trial. There is also an inter- and intra-species difference. Many patients who have been studied were also receiving digitalis: digitalis alters myocardial contractility. Moreover, the study of patients with different pathological conditions collectively known as 'cardiac disease' has made a comparative evaluation difficult: some patients had valvular dysfunction, others had abnormal myocardial contractility with or without regional asynergy, while the effect of a beta-blocking agent on ventricular function is difficult to assess in patients who also have atrial fibrillation, since atrioventricular conduction and the rate of ventricular response are also altered by the beta-blocker.

Present study

We selected for study control subjects and two groups of patients in whom beta adrenergic blockade is commonly used for the relief of angina and the control of arrhythmias. The isoprenaline response in 4 patients before and after administration of the drug indicates that effective beta-blockade was produced.

There was a negative chronotropic effect both after 10 mg and after 30 mg Sectral. Left ventricular contractility was altered and there was a fall in LVdp/dt, peak V_{ce}, and V_{max}. The mean arterial pressure was slightly reduced and LV end-diastolic pressure slightly raised: in patients with left ventricular asynergy, the arterial pressure rose marginally and the LV end-diastolic pressure was significantly increased, a consequence of the regional fibrosis of the ventricle. The net effect of these changes was a small decrease in stroke index in all three groups of patients and a fall in cardiac index which was small in the patients with cardiac disease but slightly greater in the normal subjects who had a higher resting cardiac index. The changes in contractility and cardiac output produced by Sectral are less obvious than those produced by propranolol, but greater than those of practolol (May and Baker, 1971, personal communication; Finegan *et al.*, 1972; Gibson and Coltart, 1972).

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